In the specification

On Page 7, lines 5-7 replace the paragraph as follows:

Figure 1 shows the (-) sTRSV RNA substrate-catalyst complex that fits the "hairpin" model of catalytic RNA in accordance with the present invention. (SEQ ID NOS. 56-58).

On page 7, lines 8-9 replace the paragraph as follows:

Figure 2 shows minimum energy folding of (-) sTRSV RNA (SEQ ID NO. 59).

On page 7, lines 29-31 replace the paragraph as follows:

Figures 11A-C show that there is no effect on catalytic activity when base A at position 49 in the substrate is changed to a G, U or C. (SEQ ID NOS. 60-62).

On page 8, lines 1-3 replace the paragraph as follows:

Figures 13A and 13B shows that an RNA sequence found in tobacco mosaic virus can be cleaved at a specific site with the catalytic RNA of the present invention (SEQ ID NOS. 65 and 66).

On page 8, lines 4-11 replace the paragraph as follows:

Figures 14A-C show three substrates having sequences found in the sequence of the messenger RNA coding for chloramphenicol acetyl transferase. FIGS. 14A-C also show the separation patterns on acrylamide gels of the reaction products obtained by reacting these substrates with catalytic RNAs designed to base pair with the substrates in the regions flanking the AGUC cleavage sequence (SEQ ID NOS. 67-69).

On page 8, lines 15-19 replace the paragraph as follows:

Figures 15A-15C also shows the separation patterns on acrylamide gels of the reaction products obtained by reacting this substrate with a catalytic RNA designed to base pair with the substrate in the regions flanking the CGUC cleavage sequence of the substrate (SEQ ID NO. 70).

On page 8, lines 20-27 replace the paragraph as follows:

Figures 16A and 16B shows the sequence of a substrate having a sequence found in the sequence coding for the regulatory tat protein of the HIV-1 virus. FIGS. 16A and 16B also shows the separation patterns on an acrylamide gel of the reaction products obtained by reacting this substrate with a catalytic RNA designed to base pair with the substrate in the regions flanking the UGUC cleavage sequence of the substrate (SEQ ID NO. 71).

On page 8, lines 28-36 replace the paragraph as follows:

FIGS. 17A-17B shows the sequence of a substrate having four non-native U's added to the 3' end of the sequence of the native (-) sTRSV substrate shown in FIG. 1. FIGS. 17A-17B also shows the separation patterns on an acrylamide gel of the reaction products obtained by reacting this substrate with different concentrations of a catalytic RNA designed to base pair with the substrate in the regions flanking the cleavage sequence of the substrate, including with the four non-native U's (SEQ ID NO. 72).

On page 9, lines 1-3 replace the paragraph as follows:

Figure 18 summarizes the sequence requirements for the target region of the substrate RNA. Only GUC is required for cleavage (SEQ ID NOS. 73, 74).

On page 9, lines 12-17 replace the paragraph as follows:

Figures 20A and 20B shows the RNA sequence of an autocatalytic cassette that has utility in terminating transcription at a very specific site. FIGS. 20A and 20B also shows the separation pattern on an acrylamide gel of the reaction products obtained when this catalyst was transcribed and cleaved autocatalytically (SEQ ID NO. 75).

On page 9, lines 33-34 replace the paragraph as follows:

Figure 23: Map of the pMHC-CAT mammalian expression vector (SEQ ID NO. 76).

On page 9, line 35 replace the paragraph as follows:

Figure 24: Map of plasmid pHC19R (SEQ ID NO. 77).

On page 10, lines 19-20 replace the paragraph as follows:

Figure 29: Conservation of the HIV-1 target sequence in various HIV isolates (SEQ ID NOS. 78-81).

On page 10, lines 21-24 replace the paragraph as follows:

Figure 30: Sequences of HIV-1 substrate ("SHIV") containing the conserved target sequence and of an engineered "hairpin" catalytic RNA ("RHIV") designed to cleave the substrate (SEQ ID NOS. 82, 83).

On page 10, line 29 replace the paragraph as follows:

Figures 34A and 34B: Map of pHR and partial sequence (SEQ ID NO. 84).

On page 10, lines 33-34 replace the paragraph as follows:

Figure 36: Map of pMSGRHIV and partial sequence (SEQ ID NO. 85).

On page 10, lines 35-36 replace the paragraph as follows:

Figure 37: Map of plasmid pMRHPT and partial sequence (SEQ ID NO. 86).

On page 11, lines 6-7 replace the paragraph as follows:

Figure 40: Map of the plasmid pMCATRCAT and partial sequence (SEQ ID NO. 87).

On page 11, lines 14-15 replace the paragraph as follows:

Figure 42D: A more refined secondary structure model for the (-) sTRSV RNA substrate-catalyst complex (SEQ ID NOS. 88,89).

On page 11, lines 16-20 replace the paragraph as follows:

Figure 43: Separation patterns on an acrylamide gel of the reaction products obtained by reacting substrate with "hairpin" catalytic RNA having the loop that closes the "hairpin" replaced by the sequence GGAC(UUCG)GUCC (SEQ ID NO. 90).

On page 13, lines 28-36 replace the paragraph as follows:

Figure 7. Eadie Hofstee plot of catalytic RNA R51 cleavage of substrate RNA S10. The substrate S10 containing the RNA sequence: GACAGUCCUG (SEQ ID NO. 2) was prepared from a DNA template containing the T-7 promoter as described in Example 2. This substrate was mixed with the catalytic RNA, R51, from Example 2 under standard conditions: 37.degree. C. in 12 mM MgCl.sub.2, 40 mM Tris pH 7.5 and 2 mM spermidine for 10 min. Concentrations of substrate used were as follows: 0.115 uM, 0.77 uM, 0.038 uM, 0.029 uM,

On page 15, lines 10-26 replace the paragraph as follows:

Figures 12A and 12B. Different target RNA sequences can be used as long as the base pairing is maintained with the catalytic RNA. The C:G base pair predicted by the "hairpin" model of the catalytic complex of (-) sTRSV, FIG. 1, was changed to a G:C base pair (circled) and activity was maintained. In this experiment the usual substrate S17 was not used; instead a new substrate was used with the exact same sequence except the first two vector bases GC were eliminated. The resulting sequence of this new substrate S15 was gUGACAGUCCUGUUU (SEQ ID NO. 3).

On page 22, lines 14-20 replace the paragraph as follows:

Figure 30: Sequence of HIV-1 substrate ("SHIV") having the target sequence of FIG. 28 plus additional GCG vector bases at its 5' end. Also shown is the sequence of engineered "hairpin" catalytic RNA ("RHIV") designed to cleave this substrate. The catalytic RNA also has additional 5' vector bases 3'-CUGAGGG-5' as shown (SEQ ID NO. 91).

On page 24, lines 26-30 replace the paragraph as follows:

Figure 43: Separation patterns on an acrylamide gel of the reaction products obtained by reacting substrate with a "hairpin" catalytic RNA having the loop that closes the "hairpin" replaced by the hairpin sequence GGAC(UUCG)GUCC (SEQ ID NO. 1).

On page 26, lines 29-36 replace the paragraph as follows:

L.sub.1 is a short sequence of bases which preferably has the sequence 5'-AGAA-3' when CS has the sequence 5'-NGUC-3'. Further, when L.sub.1 is 5'-AGAA-3' and CS is 5'-NGUC-3', then

the first base pair between F.sub.1 and F.sub.4 adjacent to CS and L.sub.1 is preferably G:C or C:G (see FIG. 42D and Example 32). Accordingly, a preferred target sequence in a selected substrate contains the sequence 5'-SNGUC-3', wherein S is G or C (SEQ ID NO. 92).

On page 27, lines 32-36 and page 28, replace the paragraph as follows:

P.sub.1 and P.sub.4 each is preferably from 3 to 6 bases in length, and most preferably P.sub.1 has the sequence 5'-ACCAG-3' (SEQ ID NO. 93) and P.sub.4 has the sequence 5'-CUGGUA-3' (SEQ ID NO. 94). It has been found that the A at the 5' end of 5'-ACCAG-3' (SEQ ID NO. 93) (underlined) is not base paired to the U at the 3' end of 5'-CUGGUA-3' (SEQ ID NO. 93)(underlined), and the unpaired A may act as

On page 28, lines 5-7, replace the paragraph as follows:

S1 and S2 each preferably is from 4 to 9 bases in length, and most preferably S1 has the sequence 5'-AGAAACA-3' (SEQ ID NO. 95) and S.2 has the sequence 5'-GUAUAUUAC-3' (SEQ ID NO. 96).

On page 28, lines 11-14, replace the paragraph as follows:

Finally, L2 is preferably at least 3 bases in length and preferably has the sequence 5'-GUG-3'. Further, 5'-S1-P2-L2-3' preferably has the sequence 5'-AGAAACACACGUU-3' (SEQ ID NO. 4).

On page 28, line 20, replace the paragraph as follows:

5'-F3-L1-F4-ACCAGAGAAACACACGUUGUGGUAUAUUACCUGGUA-3' (SEQ ID NO. 5)

On page 28, lines 27-28, replace the paragraph as follows:

The most preferred sequence for 5'-P2-L2-P3-3' is 5'-CACGGACUUCGGUCCGUG-3' (SEQ ID NO. 6) (see Example 32).

On page 29, lines 12-18, replace the paragraph as follows:

wherein, F1, F2, F3, F4, L1, L2, S1, S2, P1, P2, P3 and P4 are as defined above. L3 is a sequence of unpaired bases, and L.sub.3 preferably has the sequence 3'-CCUCC-5' (SEQ ID NO. 97). Thus, the molecule contains a substrate portion (5'-F1-CS-F2-3') and a catalytic portion (5'-F3-L1-F4-P1-S1-P2-L2-P3

-S2-P4-3') covalently linked together by L3 so as to produce a synthetic autocatalytic RNA catalyst.

On page 34, lines 3-19, replace the paragraph as follows:

The reaction takes place at physiological temperatures, preferably 16.degree. C. to 45.degree. C., with a temperature optimum at 37.degree. C. as described in Example 6. Temperatures above about 45.degree. C. inactivate the reaction. However, the temperature optimum of the reaction is affected by the degree of base pairing between the substrate and catalyst (see Example 18). In particular, the length of the region of the catalyst that base pairs with the 3' region of the substrate flanking the cleavage sequence can be varied so that an engineered catalyst reacting at a desired temperature can be obtained (see Example 18). Further, a "hairpin" catalyst which is more thermal stable than the native (-) sTRSV catalyst can be prepared by deleting the loop that closes the "hairpin" (Loop III in FIG. 42D) and inserting therefor the stable hairpin sequence 5-GGAC(UUCG)GUCC-3' (SEQ ID NO. 1) (see Example 32).

On page 35, lines 19-23, replace the paragraph as follows:

An active ribozyme is produced when Helix 4 is extended and the sequence of the loop that closes the "hairpin" (Loop III in FIG. 42D) is changed. As shown in FIG. 42A, Loop III was replaced with the common and very stable RNA hairpin sequence 5'-GGAC(UUCG)GUCC-3' (SEQ ID NO. 1).

On page 47, lines 1-3, replace the paragraph as follows:

catalytic RNA R51: 3'-ATTATGCTGAGTGATATCTTTGTCTCTTCAGTT-GGTCTCTTTGTGTGCAACACCATATAATGGACCAT-5 ' (SEQ ID NO. 8), and substrate RNA S17: 3'-ATTATGCTGAGTGATATCGCACTGTCAGGACAAA-5' (SEQ ID NO. 9).

On page 47, lines 35-36, replace the paragraph as follows:

##STR5## (SEQ ID NO. 10).

On page 55, lines 7-18, replace the paragraph as follows:

An RNA sequence found within the sequence of tobacco mosaic virus was synthesized using the methods described in Example 2. This synthesized target RNA had the sequence 5'gAAACAGUCCCCAAC 3' (SEQ ID NO. 11). A catalytic RNA was

synthesized with the sequence 5'-GUUGGGAGAAGUUUACCAGAGAAACACACGUUGUGGUAUAUUACCUGGUA-3' (SEQ ID NO. 12) selected so that base pairing between the substrate and the catalytic RNA is maintained in the "hairpin" configuration (see FIG. 13). When these two RNAs were mixed under standard catalytic conditions as described in Example 3, the target was cleaved demonstrating that a sequence found within a native viral RNA can be cleaved.

On page 55, lines 21-27, replace the paragraph as follows:

Three RNA sequences found within the sequence of the messenger RNA for the enzyme chloramphenicol acetyl transferase (CAT) were synthesized using the methods described in Example 2. The synthesized substrate RNAs had the sequences (A) gUUUCAGUCAGUUGC; (B) gUUUCAGUCAGUUGCUC; and (C) gggUUUCAGUCAGUUGCUCAA (see FIG. 14) (SEQ ID NOS. 13-15).

On page 75, line 8, replace the paragraph as follows:

5'-GGAATTCACC CGTCAGTTTT TAATACTGC-3' (SEQ ID NO. 16)

On page 75, line 12, replace the paragraph as follows:

5'-TGGATCCATT CTAGTATTTTG AGCTTCT-3' (SEQ ID NO. 17)

On page 81, line 8, replace the paragraph as follows:

AUUCC*GUCAUGGCGA (SEQ ID NO. 18)

On page 88, Table 1, lines 9-45, replace the paragraph as follows:

1 gcg UGAC A*GUC CUGUUU (SEQ ID NO. 10)

2 gcg UGAC A*GUC CUGUUUUUUU (SEQ ID NO. 20)

3 gcg UGAC A*GUC CUGUUUUUUUCGC (SEQ ID NO. 21)

4 gcg UGUC A*GUC CUGUUU (SEQ ID NO. 22)

5 gcg UGAG A*GUC CUGUUU (SEQ ID NO. 23)

6 g AAAC A*GUC CCCAAC (SEQ ID NO. 24)

7 g UUUC A*GUC AGUUGC (SEQ ID NO. 25)

8 gcg UUUC A*GUC AGUUGCUCAA (SEQ ID NO. 26)

9 gcg CCCC U*GUC CCCGAG (SEQ ID NO. 27)

10 gcg UGGG U*GUC GACAUAgc (SEQ ID NO. 28)

11 gcg UGAC A*GUC GUGUUU (SEQ ID NO. 29)
12 gcg UGAC A*GUC AUGUUU (SEQ ID NO. 30)
13 gcg AGAG C*GUC GGUAUUAA (SEQ ID NO. 31)
14 gcg AGAG C*GUC GGUAUUAAGCGG (SEQ ID NO. 32)
15 gcg AGAG C*GUC GGUAUUAAGC (SEQ ID NO. 33)
16 gcg UUUC U*GUC GUUUAACU (SEQ ID NO. 34)
17 gcg UGAC U*GUC CUGUUU (SEQ ID NO. 35)
18 gcg UGAC C*GUC CUGUUU (SEQ ID NO. 36)
19 gcg UGAC G*GUC CUGUUU (SEQ ID NO. 37)
20 gcg UGCC C*GUC UGUUGUGUGA (SEQ ID NO. 38)
21 gcg UGCC C*GUC UGUUGUGU (SEQ ID NO. 39)
22 gcg CCAC U*GUC GAUCGA (SEQ ID NO. 40)
23 gcg CCAC U*GUC GAUCGAG (SEQ ID NO. 41)
24 gcg AUUC C*GUC AUGGCGA (SEQ ID NO. 42)
25 gcg AUUC C*GUC AUGGC (SEQ ID NO. 43)
26 gcg AUGC G*GUC ACUCAUUA (SEQ ID NO. 44)
27 gcg AUGC G*GUC ACUCAU (SEQ ID NO. 45)
28 gcg AUCC U*GUC CAUUCAA (SEQ ID NO. 46)
29 gcg AUCC U*GUC CAUUCAAG (SEQ ID NO. 47)
30 gcg UUGG U*GUC GACCUGAA (SEQ ID NO. 48)
31 gcg ACAG C*GUC UGCUCC (SEQ ID NO. 49)
32 gcg UUGC G*GUC GCUACG (SEQ ID NO. 50)
33 gcg UUGC G*GUC GCUACGUC (SEQ ID NO. 51)
34 gcg UCUC A*GUC ACUAUG (SEQ ID NO. 52)
35 gcg CACC U*GUC ACAUAA (SEQ ID NO. 53)
36 gcg CACC U*GUC ACAUAAUU (SEQ ID NO. 54)
37 gc GUGG U*GUC UGUGGA (SEQ ID NO. 55)

On page 91, line 1-2, replace paragraph as follows:

Loop III was replaced with the common and very stable RNA hairpin sequence 5'-GGAC(UUCG)GUCC-3' (SEQ ID NO. 1).